REMARKS

By this amendment, claims 1, 3, 4 and 14 are amended. Support for the amendments are found at page 9, ll. 22-27, page 10, and page 22-23. Claim 2 is canceled. New claim 33-44 have been added. Support for the new claims can be found in the specification and originally filed claims as follows: 33-34 (original claim 3 and specification page 45, ll. 17-23 and page 53, ll. 26-27); 35-37 (page 61, ll. 20-22 and page 62, ll. 16-26); 37-38 (page 42, ll. 4-23, and page 44, ll. 19-21); 39-40, 43 (page 49, ll. 13-16); 44 (page 55, ll. 11-13); 42-43 (page 47, ll. 7-27).

Therefore, claims 1, 3-4, 8-15, 20-21, 23-29 and 33-44 are pending.

Objections to the Specification and Claims

The specification is objected to for containing references to hyperlinks, and for improperly depicting trademarks.

Claim 4 is objected to for being a duplicate of claim 3. To address this rejection, claim 4 is herein amended to recite an ATF2 peptide of about 50-75 in lieu of 50-100 recited in claim 3. Support for this amendment is found in the specification at page 4.

Claim Rejections Under 35 U.S.C. §112-Written Description

Claims 1, 2, 8-13, 15, 20, 21 and 23-29 stand rejected for reciting the phrase "inhibiting transcriptional activity of ATF2." The Examiner contends that this phrase encompasses numerous undescribed agents including antibodies, small organic molecules, and ligands. Thus, the Examiner concludes that the specification does not convey that the inventors had possession of the claimed method.

By this amendment, claim 1 is amended to recite that the ATF2 transcriptional inhibitors are selected from a polypeptide comprising an inhibitory N-terminal antagonist fragment of ATF2, an *ATF2*-specific antisense oligonucleotide, an *ATF2*-specific ribozyme, an ATF2-specific

antibody, or an expression vector encoding the inhibitory ATF2 N-terminal antagonist fragment. Support for this amendment is found in the specification at pages 9-10 and 22-23.

Whether a patent meets the written description requirement depends primarily on an interpretation of the **patent specification** and the claims in question. The description requirement is fulfilled when the patent specification conveys with reasonable clarity to a person skilled in the art, as of the filing date, the full scope of the invention, as *claimed, i.e.,* there is adequate direction to one of ordinary skill of how to obtain it. *Kennecott v. Kyocera*, 835 F.2d 1419, 1422 (Fed. Cir. 1987); *In re Hayes Microcomputer, Inc. Patent Litigation*, 982 F.2d 1527, 1534 (Fed. Cir. 1992). It is asserted that the instant specification's description of the claimed AFT2 transcriptional inhibitors meets the written description requirement.

The Examiner also rejects claims 2, 13, 15, 20, 21 and 23-29, which are directed to an inhibitory ATF2 N-terminal fragment. The Examiner contends that, to support such a generic term, the specification must sufficiently describe a representative number of species. However, the Examiner points out that the specification teaches only four N-terminal peptides (1-50; 50-100; 100-150; and 150-200), and that not all of them have inhibitory activity.

By this amendment, claim 1 is amended to recite an **inhibitory** N-terminal ATF2 fragment. Applicants respectfully traverse this rejection and submit that the term "inhibitory N-terminal ATF2 fragment" is sufficiently supported by the specification. The Examiner's attention is directed to the specification at page 9, lines 22-27, which explicitly defines the ATF2 N-terminal fragment as follows:

> ...the term "inhibitory ATF2 N-terminal fragment" refers to an N-terminal polypeptide fragment of ATF2 that inhibits ATF2 activity, and which excludes full-length ATF2. Based on the ability of specific fragments to mediate ATF2 inhibition, the inhibitor fragment comprises from about amino acid residue 50 to about amino acid residue 75, i.e., about a 25 amino acid peptide. In exemplified embodiments, a 30 amino acid residue peptide (45-75),

a 50 amino acid residue peptide (50-100), and a 115 amino acid residue peptide (1-115) were found to inhibit ATF2 activity.

Applicants are well aware of the written description requirements and the holding in *Eli Lilly,* 119 F.3d 1559 (Fed. Cir. 1997). This case held that the written description of rat cDNA for insulin did not meet the written description for cDNA encoding human insulin. Applicants fail to see how this case applies to the present application, which discloses N-terminal peptide sequences from an ATF2 N-terminal amino sequence that is **already known**. Accordingly, withdrawal of this rejection is requested. Regarding the *Lilly* holding, the Federal Circuit clarified *Enzo Biochem*, 296 F.3d at 1334 that *Lilly* did not hold that all functional descriptions of genetic material necessarily fail as a matter of law to meet the written description requirement; the requirement may be satisfied if in the knowledge of the art the disclosed function is sufficiently correlated to a particular known structure. The Federal Circuit applied this distinction in *Amgen v. Hoechest Marion Roussel, Inc.*, 314, F.3d. 1313 (2003) where the claim terms were not new or unknown biological materials that ordinary skilled artisans would not miscomprehend (at 1332).

Accordingly, withdrawal of this rejection is respectfully requested.

The Examiner next reasons that only the peptides containing the region comprising the p38 and JNK phosphorylation sites (amino acids 69 and 71) would be inhibitory, i.e., ATF2 50-100. The Examiner points to the specification, and prior art which describes the lack of activity of ATF2 69 and 71 mutants, to support his contention.

Applicants traverse this rejection and submit that it is erroneous. The specification does **not** indicate that only the regions comprising the p38 and JNK phosphorylation sites can inhibit tumor growth. Note that the specification discloses that peptide IV, which comprises ATF2 150-200 and lacks amino acids 69 and 71, has inhibitory activity in combination with chemotherapeutics. Additional rebuttal evidence is found in a commonly-owned application

recently filed in October of 2004, which is directed to a 10 amino acid ATF2 inhibitory peptide which also lacks amino acids 69 and 71.

Claim Rejections Under 35 U.S.C. §112-Enablement

Claims 1 and 8-12 also stand rejected for lack of enablement for the phrase "inhibiting transcriptional activity of ATF2." The Examiner contends that while the specification is enabling for inhibiting transcriptional activity of ATF2 using peptide 50-100, it is not enabling for inhibition of activity using the numerous undescribed agents including small organic molecules, and ligands.

It is submitted that the amendment to claim 1 obviates this rejection by reciting explicit ATF2 inhibitors. It was well within the purview of ordinarily skilled artisan to make and used the described inhibitors in claim 1 as of February 2002. The enablement requirement is met when the specification teaches a person of ordinary skill in the art how to make and use the claimed invention, without resort to "undue experimentation." *Minnesota Mining and Manufacturing Co. v. Chemique, Inc.*, 303 F.3d 1294, 1301 (Fed. Cir. 2002). A disclosure is enabling if the uncertainties are relatively limited and reasonable, as when they fall within the routine design choices of the ordinary practitioner. *Enzo Biochem, Inc. v. Gen-Probe, Inc.* 296 F.3d 1316 (Fed. Cir. 2002).

It is submitted that making N-terminal inhibitory ATF2 peptides, antisense oligonuleotides, ribozymes and antibodies, based upon known ATF2 nucleic acid and polypeptide sequences, was well known and routine for any graduate student to achieve as of the filing date of this application.

Accordingly, withdrawal of this rejection is respectfully requested.

Claim Rejections Under 35 U.S.C. §102(e)-Anticipation

Claims 1-4, 8-10, 12-14, 20, 23-26 and 29 stand rejected as allegedly anticipated by U.S. Patent 6,579,856, as evidenced by van Dam et al. (*EMBO J.* 1995; 14: 1798-1811). The Examiner contends that the '856 patent discloses a method for treating a tumor by increasing the sensitivity of the tumor cells to cancer therapy by inhibiting ATF2 transcriptional activity.

The '856 patent describes inhibitors of stress-activated protein kinases (SAPK or JNK). The specification teaches that activation of one or more of SAPK is associated with induction of various genes including *ATF2* (col. 5, ll. 13-18), and that SAPK activity can be inhibited by expressing a dominant negative ATF2 protein which is unable to be phosphorylated, hence, activated, by SAPK (col. 12, ll. 18-21; citing to the van Dam article, *supra*). The SAPK inhibitors, including dominant negative ATF2 are described as useful for treating or sensitizing cancer cells, including melanoma and breast cancer cells, to chemotherapy (col. 15, l. 55, to col. 16, l. 29). Exemplary inhibitors are antisense/ribozyme SAPK's, dominant negative c-jun or ATF2 polypeptides, and anti-SAPK-antibodies.

By this amendment, claim 1 is amended to recite specific ATF2 inhibitors and does not encompass a dominant negative ATF2. According to the above-cited definition in the specification, an inhibitory ATF2 N-terminal fragment *excludes* full-length ATF2. As the Examiner is well aware, a determination that a claimed invention is anticipated requires a showing that each element of a claim is found, either expressly or under principles of inherency, in a **single** prior art reference, or that the claimed invention was previously known or embodied in a single prior art device, product, or method. *Schering Corp. v. Geneva Pharm., Inc.*, 339 F.3d 1373, 1377 (Fed. Cir. 2003). Since the '856 reference does not disclose any of the ATF2 inhibitors recited in the present claims, as amended, much less the specific ATF2 inhibitors disclosed, it is submitted that this references does not anticipate the pending claims.

The claims were also rejected over the van Dam reference alone. van Dam discloses that c-jun and its dimer partners such as ATF2 are essential for the response of cells to genotoxic agents, and that c-jun (-/-) cells are resistant to UVC irradiation. van Dam further discloses that a dominant negative ATF2, mutated at amino acid residues 69 and 71, phosphoacceptor sites, or a deletion mutant lacking the transactivation domain, was unable to be activate transcription upon treatment by UV radiation in HeLa cells or transformed fibroblasts.

Contrary to the Examiner's contention, van Dam's deletion mutant **does not** comprise ATF2 residues 19-96. This region is the minimal transactivation domain in plasmid pGEX-ATF-2-N, as indicated in the materials and methods, on page 1809, col. 2. The deletion mutant plasmid designated Gal4-d4ATF-2 (see page 1804, Figure 3) according to van Dam **lacks** this transactivation domain (page 1801, col. 2, third full paragraph). Accordingly, van Dam certainly does not teach an ATF2 inhibitory peptide comprising ATF2 50-100, much less for the sensitization of tumor cells to UV radiation.

In view of the foregoing, van Dam does not anticipate the present claims and withdrawal of this rejection is respectfully requested.

Claim Rejections Under 35 U.S.C. §103-Obviousness

Claims 1, 10, 11, 23, and 26-28 stand rejected as obvious over the '856 patent, as evidenced by the van Dam article, in view of Ivanov et al. (*Oncogene*. 2000; 19: 3002-12). According to the Examiner, the '856 patent, as evidenced by van Dam, renders obvious the claims to using an inhibitory N-terminal ATF2 fragment to treat a tumor. The Examiner further contends that while the '856 patent does not teach using an ATF2 inhibitor in combination with p38 inhibitor SB203580, Ivanov teaches that this inhibitor sensitizes tumors to UV-induced death.

Applicants respectfully traverse this rejection. In order for a reference or combination of references to render a claim obvious, there must be some motivation or suggestion in the prior

art, taken as a whole, to combine the references. See, *e.g., In re Beattie* , 974 F.2d 1309, 1311 (Fed. Cir. 1992). As described above, the '856 discloses using a full length, dominant negative ATF2 mutated at amino acid residue to sensitize cancer cells to UV death, and van Dam discloses that a mutant, ATF2 deletion mutant, cannot be activated *in vitro* by UV. van Dam thus concludes that the N-terminal 112 amino acids, explicitly amino acid residues 69 and 71, the phosphoacceptor sites, are required and sufficient for ATF2's transactivating function.

The foregoing prior art does not teach the use of any other ATF2 inhibitors except full length ATF2 mutated at residues 69 and 71, or ATF2 deletion mutants, neither of which are encompassed by the present claims. Moreover, van Dam does not teach or suggest using the ATF2 deletion mutant as therapy, much less for cancer therapy. To the contrary, use of van Dam's deletion mutant lacking the transactivation domain (residues 19-96) would *not* inhibit endogenous ATF2-mediated transcription. Similarly, while the '856 patent discloses other inhibitors for SAPKs, including antisense, ribozymes and antibodies, it does not disclose inhibition ATF2 using these inhibitors. As indicated above, on the dominant-negative ATF2 is disclosed. If the '856 inventors had contemplated or suggested use of antisense or ribozymes to inhibit ATF2, they would have disclosed this along with use of those agents to inhibit the SAPKs. To the contrary, it appears that the '856 inventors were mainly concerned with inhibiting the activity of the SAPKs that phosphorylated ATF2, not with inhibiting ATF2 itself.

In addition, neither reference discloses the use of inhibitory N-terminal ATF2 peptides to sensitize cancer cells to radiation. In fact, the '856 patent teaches the opposite by teaching that a mutant ATF2 lacking amino acids 19-96 cannot activate transcription. Accordingly, there can be no proper combination of the references to render obvious claims to these peptides since the requisite motivation to combine is not provided by the references.

Moreover, present invention unexpectedly demonstrates that ATF2 inhibitory peptides that **do not** affect phosphorylation of residues 69 and 71 also inhibit ATF2 activity. This also is in contrast to the prior art teachings that these any inhibitor must abrogate phosphorylation

of these residues. Accordingly, since the prior art teaches away from the present invention, the can be no finding of obviousness.

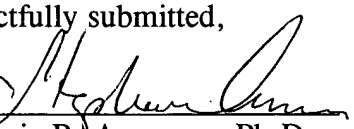
Lastly, Ivanov's disclosure of the p38 inhibitor SB203580 as sensitizing cells to UV-induced death, in combination with the '856 patent or van Dam, does not render the claims obvious. Ivanov discloses that inhibiting p38, a kinase which phosphorylates ATF2, increases UVC-induced apoptosis in melanoma cells. There is no suggestion of using a combination therapy with the p38 inhibitor and an ATF2 inhibitor as claimed, despite that Ivanov also teaches that ATF2 mutants lacking the transactivation domain also increased the resistance of cells to UVC-radiation. To the contrary, the paper focuses on the unique mechanisms of how inhibiting p38 elicits the increased sensitivity to cell death. As above with the '856 patent, the absence of suggestion of a combination, where such a combination could have been disclosed in view of the stated knowledge in the art, is strong support for non-obviousness.

In view of the forgoing, withdrawal of this rejection is respectfully requested.

In view of the above amendment, applicant believes the pending application is in condition for allowance.

Dated: March 20, 2005

Respectfully submitted,

By 

Stephanie R. Amoroso, Ph.D.
Registration No.: 51,401
DARBY & DARBY P.C.
P.O. Box 5257
New York, New York 10150-5257
(212) 527-7700
(212) 527-7701 (Fax)
Attorneys/Agents For Applicant